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 NEWS  1          Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2  Sep 29  The Philippines Inventory of Chemicals and Chemical
                  Substances (PICCS) has been added to CHEMLIST
 NEWS  3  Oct 27  New Extraction Code PAX now available in Derwent
                  Files
 NEWS  4  Oct 27  SET ABBREVIATIONS and SET PLURALS extended in
                  Derwent World Patents Index files
 NEWS  5  Oct 27  Patent Assignee Code Dictionary now available
                  in Derwent Patent Files
 NEWS  6  Oct 27  Plasdoc Key Serials Dictionary and Echoing added to
                  Derwent Subscriber Files WPIDS and WPIX
 NEWS  7  Nov 29  Derwent announces further increase in updates for DWPI
 NEWS  8  Dec  5  French Multi-Disciplinary Database PASCAL Now on STN
 NEWS  9  Dec  5  Trademarks on STN - New DEMAS and EUMAS Files
 NEWS 10  Dec 15  2001 STN Pricing
 NEWS 11  Dec 17  Merged CEABA-VTB for chemical engineering and
                  biotechnology
 NEWS 12  Dec 17  Corrosion Abstracts on STN
 NEWS 13  Dec 17  SYNTHLINE from Prous Science now available on STN
 NEWS 14  Dec 17  The CA Lexicon available in the CAPLUS and CA files
 NEWS 15  Jan 05  AIDSLINE is being removed from STN
 NEWS 16  Feb 06  Engineering Information Encompass files have new names
 NEWS 17  Feb 16  TOXLINE no longer being updated

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FILE 'HOME' ENTERED AT 10:07:42 ON 29 MAR 2001

=> file medline caplus embase biosis
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                 ENTRY    SESSION
FULL ESTIMATED COST                               0.15       0.15

FILE 'MEDLINE' ENTERED AT 10:07:58 ON 29 MAR 2001

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FILE 'BIOSIS' ENTERED AT 10:07:58 ON 29 MAR 2001
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=> s (factor IXa) or (Factor IX)
L1       12853 (FACTOR IXA) OR (FACTOR IX)

=> s l1 (P) (mutat? or inhib?)
L2        3660 L1 (P) (MUTAT? OR INHIB?)

=> s l2 (P) clot or thromb?
L3      652552 L2 (P) CLOT OR THROMB?

=> s l2 (P) (clot or thromb?)
L4        1125 L2 (P) (CLOT OR THROMB?)

=> s l2 (P) (inhibit? (5N) (clot or thromb?))
L5         355 L2 (P) (INHIBIT? (5N) (CLOT OR THROMB?))

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'199609' NOT A VALID FIELD CODE
'199609' NOT A VALID FIELD CODE
'199609' NOT A VALID FIELD CODE
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L6           0 L5 AND @PD<199609

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'1999609' NOT A VALID FIELD CODE
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'1999609' NOT A VALID FIELD CODE
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L7           0 L5 AND @PD<1999609

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'1999609' NOT A VALID FIELD CODE
'1999609' NOT A VALID FIELD CODE
L8           0 L5 AND @PD <1999609
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'1999609' NOT A VALID FIELD CODE
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'1999609' NOT A VALID FIELD CODE
'1999609' NOT A VALID FIELD CODE
L9            0 L5 AND @PD < 1999609

=> s l5 and PD<1999609
'1999609' NOT A VALID FIELD CODE
DATE SPECIFICATION IS NOT VALID
DATE SPECIFICATION IS NOT VALID
DATE SPECIFICATION IS NOT VALID
Date specifications may use ranges and numeric operators.  The date
itself can be in any of the following general formats:

   STN Format:     YYYYMMDD

   Slash Format:   MM/DD/YYYY or MM/YYYY

   Dot Format:     DD.MM.YYYY or MM.YYYY

   Text Format:    February 10, 1987       Feb 1989
                   Feb. 10, 1987           1990
                   Feb. 10, 2000           1998 - 2001
                   Feb 10, 1987            July 1997 - May 2002
                   10 February 1987        March 5 - 8, 1990
                   10 Feb 2007             April - June, 1999

   Any year entered with only two digits will be interpreted as being
   in the range 1900-1999.  Thus, Mar 12 01 will be searched as
   19010312.

=> s l5 and PD<19990927
'19990927' NOT A VALID FIELD CODE
   2 FILES SEARCHED...
   3 FILES SEARCHED...
L10         263 L5 AND PD<19990927

=> dup rem l10
PROCESSING COMPLETED FOR L10
L11         128 DUP REM L10 (135 DUPLICATES REMOVED)

=> dis his

     (FILE 'HOME' ENTERED AT 10:07:42 ON 29 MAR 2001)

     FILE 'MEDLINE, CAPLUS, EMBASE, BIOSIS' ENTERED AT 10:07:58 ON 29 MAR 2001
L1      12853 S (FACTOR IXA) OR (FACTOR IX)
L2       3660 S L1 (P) (MUTAT? OR INHIB?)
L3     652552 S L2 (P) CLOT OR THROMB?
L4       1125 S L2 (P) (CLOT OR THROMB?)
L5        355 S L2 (P) (INHIBIT? (5N) (CLOT OR THROMB?))
L6          0 S L5 AND @PD<199609
L7          0 S L5 AND @PD<1999609
L8          0 S L5 AND @PD <1999609
L9          0 S L5 AND @PD < 1999609
L10       263 S L5 AND PD<19990927
L11       128 DUP REM L10 (135 DUPLICATES REMOVED)

=> s l11 (P) administ?
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L52 (P) ADMINIST?'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L54 (P) ADMINIST?'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L56 (P) ADMINIST?'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L58 (P) ADMINIST?'
L12         7 L11 (P) ADMINIST?

=> dis l12 1-7 ibib abs kwic

L12  ANSWER 1 OF 7  CAPLUS  COPYRIGHT 2001 ACS
ACCESSION NUMBER:        1999:794322  CAPLUS
DOCUMENT NUMBER:         132:18789
TITLE:                   Compositions and methods using an oxidized/reduced
                         low-molecular-weight heparin compound for inhibiting
                         thrombogenesis
INVENTOR(S):             Hirsh, Jack; Weitz, Jeffrey I.
PATENT ASSIGNEE(S):      Hamilton Civic Hospitals Research Development Inc.,
                         Can.
SOURCE:                  U.S., 48 pp., Cont.-in-part of U.S. 5,763,427.
                         CODEN: USXXAM
DOCUMENT TYPE:           Patent
LANGUAGE:                English
FAMILY ACC. NUM. COUNT:  4
PATENT INFORMATION:

     PATENT NO.       KIND  DATE          APPLICATION NO.  DATE
     ---------------  ----  --------      ---------------  --------
     US 6001820       A     19991214      US 1997-870528   19970606
     US 5744457       A     19980428      US 1995-540324   19951006 <--
     AU 9651400       A1    19961016      AU 1996-51400    19960329 <--
     US 5763427       A     19980609      US 1996-624327   19960329 <--
     JP 11506420      T2    19990608      JP 1996-528734   19960329 <--
     NO 9704500       A     19971128      NO 1997-4500     19970929 <--
PRIORITY APPLN. INFO.:                     US 1995-412332   19950331
                                           US 1995-540324   19951006
                                           US 1996-624327   19960329
                                           WO 1996-CA190    19960329
OTHER SOURCE(S):         MARPAT 132:18789
AB   Compns. and methods are provided for the treatment of cardiovascular
     diseases.  More particularly, the invention relates to modifying thrombus
     formation by administering an agent which, inter alia, is
     capable of (1) selectively inactivating thrombin which is bound either to
     fibrin in a clot or to some other surface, but which has only minimal
     inhibitory activity against free thrombin, i.e.,
     fluid-phase thrombin; (2) inhibiting the assembly of
     the intrinsic tenase complex, thereby inhibiting the activation
     of Factor X by Factor IXa; and (3) inhibiting
     the activation of Factor IX by Factor XIa.  The
     compns. and methods of the present invention are particularly useful for
     preventing thrombosis in the circuit of cardiac bypass app. and in
```

patients undergoing renal dialysis, and for treating patients suffering from or at risk of suffering from thrombus-related cardiovascular conditions, such as unstable angina, acute myocardial infarction (heart attack), cerebrovascular accidents (stroke), pulmonary embolism, deep vein thrombosis, arterial thrombosis, etc. The invention uses a polyanionic carbohydrate, esp. an oxidized/reduced low-mol.-wt. heparin compd. (prepn. described).

REFERENCE COUNT: 57
REFERENCE(S):
(1) Alhenc-Gelas; Fundamental and Clinical Cardiology 1994, V19, P43 CAPLUS
(2) Anon; WO 8201005 1982 CAPLUS
(3) Anon; WO 8203627 1982 CAPLUS
(4) Anon; EP 101141 1984 CAPLUS
(5) Anon; EP 121067 1987 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 6001820	A	19991214	US 1997-870528	19970606
	US 5744457	A	19980428	US 1995-540324	19951006 <--
	AU 9651400	A1	19961016	AU 1996-51400	19960329 <--
	US 5763427	A	19980609	US 1996-624327	19960329 <--
	JP 11506420	T2	19990608	JP 1996-528734	19960329 <--
	NO 9704500	A	19971128	NO 1997-4500	19970929 <--

AB Compns. and methods are provided for the treatment of cardiovascular diseases. More particularly, the invention relates to modifying thrombus formation by **administering** an agent which, inter alia, is capable of (1) selectively inactivating thrombin which is bound either to fibrin in a clot or to some other surface, but which has only minimal **inhibitory** activity against free **thrombin**, i.e., fluid-phase **thrombin**; (2) **inhibiting** the assembly of the intrinsic tenase complex, thereby **inhibiting** the activation of Factor X by **Factor IXa**; and (3) **inhibiting** the activation of **Factor IX** by Factor XIa. The compns. and methods of the present invention are particularly useful for preventing thrombosis in the circuit of cardiac bypass app. and in patients undergoing renal dialysis, and for treating patients suffering from or at risk of suffering from thrombus-related cardiovascular conditions, such as unstable angina, acute myocardial infarction (heart attack), cerebrovascular accidents (stroke), pulmonary embolism, deep vein thrombosis, arterial thrombosis, etc. The invention uses a polyanionic carbohydrate, esp. an oxidized/reduced low-mol.-wt. heparin compd. (prepn. described).

IT 37203-61-5, Blood coagulation factor XIa 37316-87-3, Blood coagulation **factor IXa**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(oxidized/reduced low-mol.-wt. heparin compd. for **inhibiting thrombogenesis**)

L12 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:619353 CAPLUS
DOCUMENT NUMBER: 131:241741
TITLE: A human antibody that binds to the .gamma.-carboxyglutamic acid domain of factor IX is a potent antithrombotic in vivo
AUTHOR(S): Refino, Canio J.; Himber, Jacques; Burcklen, Louis; Moran, Paul; Peek, Mark; Suggett, Shelley; Devaux, Brigitte; Kirchhofer, Daniel
CORPORATE SOURCE: Cardiovascular Research Antibody Technologies Dep., Genentech Inc., South San Francisco, CA, 94080, USA
SOURCE: Thromb. Haemostasis (1999), 82(3), 1188-1195
CODEN: THHADQ; ISSN: 0340-6245
PUBLISHER: F. K. Schattauer Verlagsgesellschaft mbH
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The human antibody F(ab')2, 10C12, which specifically binds to the GIa domain of **factor IX**, interfered with all known coagulation processes that involve **factor IX**/IXa. These include the function of the intrinsic Xase complex and the activation of zymogen **factor IX** by factor XIa and by the tissue factor:factor VIIa complex. 10C12 potently **inhibited** activated partial **thromboplastin** clotting times (APTT) in plasma of guinea pig and rat, thus enabling in vivo evaluation. In guinea pigs, a bolus **administration** of 10C12 (10 .mu.g/kg) prevented cyclic flow variations in damaged carotid arteries without affecting coagulation or bleeding parameters. At a 100-fold higher dose, 10C12 had no effect on normal hemostasis as assessed by the cuticle bleeding time. At this dose, 10C12 was also efficacious in a rat arterial thrombosis model, substantially reducing clot wt. and duration of vessel occlusion while prolonging ex vivo APTT only 1.2-fold. The dose of heparin required to produce comparable anti-thrombotic effects prolonged the APTT by 12-fold and increased the tail bleeding time (TBT) by 8-fold. In contrast, 10C12 had no effect on TBT. Rat tails showed a tendency for rebleeding which 10C12 exacerbated. In conclusion, the antithrombotic potency of the 10C12 antibody in 2 species provides evidence for an important role of FIX, and its GIa domain in particular, during thrombogenesis under arterial flow conditions. The relative safety at EDs of this fully human antibody suggests that it may have therapeutic value for treatment of thrombotic disorders.

REFERENCE COUNT: 45
REFERENCE(S):
(1) Ahmad, S; J Biol Chem 1989, V264, P20012 CAPLUS
(2) Ahmad, S; Trends Cardiovasc Med 1994, V4, P271 CAPLUS
(3) Baselga, J; J Clin Oncol 1996, V14, P737 CAPLUS
(4) Benedict, C; Blood 1993, V81, P2059 CAPLUS
(5) Benedict, C; J Clin Invest 1991, V88, P1760 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

SO Thromb. Haemostasis (1999), 82(3), 1188-1195
CODEN: THHADQ; ISSN: 0340-6245

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prolonging ex vivo APTT only 1.2-fold. The dose of heparin required to produce comparable anti-thrombotic effects prolonged the APTT by 12-fold and increased the tail bleeding time (TBT) by 8-fold. In contrast, 10C12 had no effect on TBT. Rat tails showed a tendency for rebleeding which 10C12 exacerbated. In conclusion, the antithrombotic potency of the 10C12 antibody in 2 species provides evidence for an important role of FIX, and its GIa domain in particular, during thrombogenesis under arterial flow conditions. The relative safety at EDs of this fully human antibody suggests that it may have therapeutic value for treatment of thrombotic disorders.

L12 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:443190 CAPLUS
DOCUMENT NUMBER: 131:208823
TITLE: Targeted inhibition of intrinsic coagulation limits cerebral injury in stroke without increasing intracerebral hemorrhage
AUTHOR(S): Choudhri, Tanvir F.; Hoh, Brian L.; Prestigiacomo, Charles J.; Huang, Judy; Kim, Louis J.; Schmidt, Ann Marie; Kisiel, Walter; Connolly, E. Sander, Jr.; Pinsky, David J.
CORPORATE SOURCE: Department of Neurological Surgery, Columbia University College of Physicians and Surgeons, New York, NY, 10032, USA
SOURCE: J. Exp. Med. (1999), 190(1), 91-99
CODEN: JEMEAV; ISSN: 0022-1007
PUBLISHER: Rockefeller University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Agents that restore vascular patency in stroke also increase the risk of intracerebral hemorrhage (ICH). As **Factor IXa** is a key intermediary in the intrinsic pathway of coagulation, targeted **inhibition** of **Factor IXa**-dependent coagulation might **inhibit** microvascular **thrombosis** in stroke without impairing extrinsic hemostatic mechanisms that limit ICH. A competitive **inhibitor** of native **Factor IXa** for assembly into the intrinsic Factor X activation complex, Factor IXai, was prepd. by covalent modification of the **Factor IXa** active site. In a modified cephalin clotting time assay, in vivo **administration** of Factor IXai caused a dose-dependent increase in time to clot formation (3.6-fold increase at the 300 .mu.g/kg dose compared with vehicle-treated control animals, $P < 0.05$). Mice given Factor IXai and subjected to middle cerebral artery occlusion and reperfusion demonstrated reduced microvascular fibrin accumulation by immunoblotting and immunostaining, reduced 111In-labeled platelet deposition (42% decrease, $P < 0.05$), increased cerebral perfusion (2.6-fold increase in ipsilateral blood flow by laser doppler, $P < 0.05$), and smaller cerebral infarcts than vehicle-treated controls (70% redn., $P < 0.05$) based on tri-Ph tetrazolium chloride staining of serial cerebral sections. At therapeutically EDs, Factor IXai was not assocd. with increased ICH, as opposed to tissue plasminogen activator (tPA) or heparin, both of which significantly increased ICH. Factor IXai was cerebroprotective even when given after the onset of stroke, indicating that microvascular thrombosis continues to evolve (and may be **inhibited**) even after primary occlusion of a major cerebrovascular tributary.
REFERENCE COUNT: 35
REFERENCE(S): (1) Benedict, C; J Clin Invest 1991, V88, P1760 CAPLUS
(4) Choudhri, T; J Clin Invest 1998, V102, P1301 CAPLUS
(5) Choudhri, T; Stroke 1997, V28, P2296 CAPLUS
(6) Connolly, E; Circ Res 1997, V81, P304 CAPLUS
(7) Connolly, E; J Clin Invest 1996, V97, P209 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT
SO J. Exp. Med. (1999), 190(1), 91-99
CODEN: JEMEAV; ISSN: 0022-1007
AB Agents that restore vascular patency in stroke also increase the risk of intracerebral hemorrhage (ICH). As **Factor IXa** is a key intermediary in the intrinsic pathway of coagulation, targeted **inhibition** of **Factor IXa**-dependent coagulation might **inhibit** microvascular **thrombosis** in stroke without impairing extrinsic hemostatic mechanisms that limit ICH. A competitive **inhibitor** of native **Factor IXa** for assembly into the intrinsic Factor X activation complex, Factor IXai, was prepd. by covalent modification of the **Factor IXa** active site. In a modified cephalin clotting time assay, in vivo **administration** of Factor IXai caused a dose-dependent increase in time to clot formation (3.6-fold increase at the 300 .mu.g/kg dose compared with vehicle-treated control animals, $P < 0.05$). Mice given Factor IXai and subjected to middle cerebral artery occlusion and reperfusion demonstrated reduced microvascular fibrin accumulation by immunoblotting and immunostaining, reduced 111In-labeled platelet deposition (42% decrease, $P < 0.05$), increased cerebral perfusion (2.6-fold increase in ipsilateral blood flow by laser doppler, $P < 0.05$), and smaller cerebral infarcts than vehicle-treated controls (70% redn., $P < 0.05$) based on tri-Ph tetrazolium chloride staining of serial cerebral sections. At therapeutically EDs, Factor IXai was not assocd. with increased ICH, as opposed to tissue plasminogen activator (tPA) or heparin, both of which significantly increased ICH. Factor IXai was cerebroprotective even when given after the onset of stroke, indicating that microvascular thrombosis continues to evolve (and may be **inhibited**) even after primary occlusion of a major cerebrovascular tributary.

L12 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:347694 CAPLUS
DOCUMENT NUMBER: 129:117633
TITLE: Heparinless cardiopulmonary bypass with active-site blocked factor IXA: a preliminary study on the dog
AUTHOR(S): Spanier, Talia B.; Oz, Mehmet C.; Minanov, Oktavijan P.; Simantov, Ronit; Kisiel, Walter; Stern, David M.; Rose, Eric A.; Schmidt, Ann Marie
CORPORATE SOURCE: Department of Surgery, Columbia University College of Physicians and Surgeons, New York, NY, 10032, USA
SOURCE: J. Thorac. Cardiovasc. Surg. (1998), 115(5), 1179-1188
CODEN: JTCSAQ; ISSN: 0022-5223
PUBLISHER: Mosby, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Cardiopulmonary bypass is a potent stimulus for activation of procoagulant pathways. Heparin, the traditional antithrombotic agent, however, is often assocd. with increased perioperative blood loss because of its

multiple sites of action in the coagulation cascade and its antiplatelet and profibrinolytic effects. Furthermore, heparin-mediated immunol. reactions (i.e., heparin-induced thrombocytopenia) may contraindicate its use. Cardiopulmonary bypass with a selective **factor IXa inhibitor** was tested to see whether it could effectively limit bypass circuit/intravascular space thrombosis while decreasing extravascular bleeding, thereby providing an alternative anticoagulant strategy when heparin may not be safely **administered**. Active site-blocked **factor IXa**, a competitive **inhibitor** of the assembly of **factor IXa** into the factor X activation complex, was prepd. by modification of the enzyme's active site by the use of dansyl glutamic acid-glycine-arginine-chlormethylketone. Twenty mongrel dogs (five were given std. heparin/protamine; 15 were given activated site-blocked **factor IXa** doses ranging from 300 to 600 .mu.g/kg) underwent 1 h of hypothermic cardiopulmonary bypass, and blood loss was monitored for 3 h after the procedure. Use of activated site-blocked **factor IXa** as an anticoagulant in cardiopulmonary bypass limited fibrin deposition within the extracorporeal circuit as assessed by SEM, comparable with the antithrombotic effect seen with heparin. In contrast to heparin, effective antithrombotic doses of activated site-blocked **factor IXa** significantly diminished blood loss in the thoracic cavity and in an abdominal incisional bleeding model. These initial studies on the dog suggest that **administration** of activated site-blocked **factor IXa** may be an effective alternative anticoagulant strategy in cardiopulmonary bypass when heparin is contraindicated, affording **inhibition** of intravascular/extracorporeal circuit **thrombosis** with enhanced hemostasis in the surgical wound.

SO J. Thorac. Cardiovasc. Surg. (1998), 115(5), 1179-1188
CODEN: JTCSAQ; ISSN: 0022-5223

AB Cardiopulmonary bypass is a potent stimulus for activation of procoagulant pathways. Heparin, the traditional antithrombotic agent, however, is often assocd. with increased perioperative blood loss because of its multiple sites of action in the coagulation cascade and its antiplatelet and profibrinolytic effects. Furthermore, heparin-mediated immunol. reactions (i.e., heparin-induced thrombocytopenia) may contraindicate its use. Cardiopulmonary bypass with a selective **factor IXa inhibitor** was tested to see whether it could effectively limit bypass circuit/intravascular space thrombosis while decreasing extravascular bleeding, thereby providing an alternative anticoagulant strategy when heparin may not be safely **administered**. Active site-blocked **factor IXa**, a competitive **inhibitor** of the assembly of **factor IXa** into the factor X activation complex, was prepd. by modification of the enzyme's active site by the use of dansyl glutamic acid-glycine-arginine-chlormethylketone. Twenty mongrel dogs (five were given std. heparin/protamine; 15 were given activated site-blocked **factor IXa** doses ranging from 300 to 600 .mu.g/kg) underwent 1 h of hypothermic cardiopulmonary bypass, and blood loss was monitored for 3 h after the procedure. Use of activated site-blocked **factor IXa** as an anticoagulant in cardiopulmonary bypass limited fibrin deposition within the extracorporeal circuit as assessed by SEM, comparable with the antithrombotic effect seen with heparin. In contrast to heparin, effective antithrombotic doses of activated site-blocked **factor IXa** significantly diminished blood loss in the thoracic cavity and in an abdominal incisional bleeding model. These initial studies on the dog suggest that **administration** of activated site-blocked **factor IXa** may be an effective alternative anticoagulant strategy in cardiopulmonary bypass when heparin is contraindicated, affording **inhibition** of intravascular/extracorporeal circuit **thrombosis** with enhanced hemostasis in the surgical wound.

L12 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:702042 CAPLUS
DOCUMENT NUMBER: 126:31658
TITLE: Peptide boronic acid inhibitors of trypsin-like enzymes
INVENTOR(S): Claeson, Goran; Philipp, Manfred H. W.; Metternich, Rainer
PATENT ASSIGNEE(S): Thrombosis Research Institute, UK
SOURCE: U.S., 13 pp. Cont. of U.S. Ser. No. 998, 632, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5574014	A	19961112	US 1994-240606	19940510 <--
US 5856306	A	19990105	US 1995-459177	19950602 <--
US 6114308	A	20000905	US 1998-79243	19980514
PRIORITY APPLN. INFO.:			US 1988-181511	19880428
			GB 1989-2304	19890202
			US 1989-406663	19890913
			US 1991-680496	19910404
			US 1991-795219	19911120
			US 1992-998632	19921230
			US 1994-240606	19940510
			US 1995-459177	19950602

OTHER SOURCE(S): MARPAT 126:31658

AB Peptide boronic acids XYNHCH[(CH2)3OR]BQ1Q2 (I; X = H, N-protecting group; Y = Phe-Pro; Q1Q2 = diol residue; R = C1-4 alkyl) are **inhibitors** of trypsinlike enzymes (including trypsin, **thrombin**, factor Xa, **factor IXa**, factor VIIa, factor XIIa, plasmin, acrosin, complement proteases, kallikrein, urokinase, and tissue plasminogen activator), and may be **administered** orally or parenterally as antithrombotics. They have a rapid onset of activity and low toxicity. Thus, benzyloxycarbonyl-D-phenylalanine p-nitrophenyl ester was condensed with proline, converted to the N-hydroxysuccinimidyl ester, coupled with the (+)-pinanediol ester of (TMS)2NCH[(CH2)3Br]B(OH)2, and reacted with guanidine-HCl and MeONa in MeOH to produce I [X = PhCH2O2C; Y = D-Phe-L-Pro; R = OMe; Q1Q2 = (+)-pinanediyl].

PI US 5574014 A **19961112**

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 5574014	A	19961112	US 1994-240606	19940510 <--
US 5856306	A	19990105	US 1995-459177	19950602 <--
US 6114308	A	20000905	US 1998-79243	19980514

AB Peptide boronic acids XYNHCH[(CH2)3OR]BQ1Q2 (I; X = H, N-protecting group;

Y = Phe-Pro; Q1Q2 = diol residue; R = C1-4 alkyl) are **inhibitors** of trypsinlike enzymes (including trypsin, **thrombin**, factor Xa, **factor IXa**, factor VIIa, factor XIIa, plasmin, acrosin, complement proteases, kallikrein, urokinase, and tissue plasminogen activator), and may be **administered** orally or parenterally as antithrombotics. They have a rapid onset of activity and low toxicity. Thus, benzyloxycarbonyl-D-phenylalanine p-nitrophenyl ester was condensed with proline, converted to the N-hydroxysuccinimidyl ester, coupled with the (+)-pinanediol ester of (TMS)2NCH[(CH2)3Br]B(OH)2, and reacted with guanidine-HCl and MeONa in MeOH to produce I [X = PhCH2O2C; Y = D-Phe-L-Pro; R = OMe; Q1Q2 = (+)-pinanediyl].

L12 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1982:223071 CAPLUS
DOCUMENT NUMBER: 96:223071
TITLE: Studies on oral **administration** of concentrated factor IX preparation
AUTHOR(S): Ueno, Masaharu; Horikoshi, Isamu; Takahashi, Kaoru; Sakuragawa, Nobuo
CORPORATE SOURCE: Dep. Hosp. Pharm., Toyama Med. Pharm. Univ., Toyama, 930-01, Japan
SOURCE: Yakugaku Zasshi (1982), 102(2), 202-6
CODEN: YKKZAJ; ISSN: 0031-6903
DOCUMENT TYPE: Journal
LANGUAGE: Japanese
AB blood-coagulation **factor IX** [9001-28-9] Was stable at 4-25.degree. in mildly alk. solns. and was effectively encapsulated in liposome prepns. contg. 5% stearylamine or 0.02 M Ca2+; oral **administration** of the liposome-entrapped **factor IX** shortened clotting time in dogs. The transformation of prothrombin [9001-26-7] into **thrombin** [9002-04-4] was **inhibited** by adding phosphatidylcholines (250 mg) or 50,000 units aprotinin [9004-04-0]. The intestinal absorption of factor II, VII [9001-25-6], IX, and X [9001-29-0] is described.
TI Studies on oral **administration** of concentrated factor IX preparation
SO Yakugaku Zasshi (1982), 102(2), 202-6
CODEN: YKKZAJ; ISSN: 0031-6903
AB blood-coagulation **factor IX** [9001-28-9] Was stable at 4-25.degree. in mildly alk. solns. and was effectively encapsulated in liposome prepns. contg. 5% stearylamine or 0.02 M Ca2+; oral **administration** of the liposome-entrapped **factor IX** shortened clotting time in dogs. The transformation of prothrombin [9001-26-7] into **thrombin** [9002-04-4] was **inhibited** by adding phosphatidylcholines (250 mg) or 50,000 units aprotinin [9004-04-0]. The intestinal absorption of factor II, VII [9001-25-6], IX, and X [9001-29-0] is described.
IT 9001-28-9
RL: BIOL (Biological study)
(liposome-entrapped, oral **administration** of)

L12 ANSWER 7 OF 7 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 87160092 EMBASE
DOCUMENT NUMBER: 1987160092
TITLE: Evaluation of p-amidinophenyl esters as potential antithrombotic agents.
AUTHOR: Pizzo S.V.; Turner A.D.; Porter N.A.; Gonias S.L.
CORPORATE SOURCE: Department of Pathology, Duke University Medical Center, Durham, NC 27710, United States
SOURCE: Thrombosis and Haemostasis, (1986) 56/3 (387-390).
CODEN: THHADQ
COUNTRY: Germany
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
030 Pharmacology
LANGUAGE: English
AB Three p-amidinophenyl esters have been synthesized and characterized as irreversible **inhibitors** of the vitamin-K dependent proteinases; **factors IXa**, Xa and thrombin. In the present report we describe the in vitro and in vivo effects of these agents on standard coagulation tests in vitro and in blood from animals treated with the compounds. At a concentration of 500 .mu.M, the three esters increased the activated partial thromboplastin time (PTT) of pooled human plasma 3 to 5-fold. The prothrombin time increased 1.4 to 3.7-fold under similar conditions. The p-amidinophenyl ester of cinnamic acid (CINN) showed the most pronounced effect on both assays. This ester also is the best **inhibitor** of human **factors IXa** and Xa, while the p-amidinophenyl ester of benzoic acid (BENZ) is a slightly better .alpha.-**thrombin inhibitor**. The effect of these esters on the thrombin clotting time correlated with in vitro kinetic measurements of .alpha.-**thrombin inhibition** rates. Both BENZ and CINN increased the assay endpoint more than 6-fold. The three esters also were studied using mouse plasma. A comparable effect on the PTT was noted. Intravenous **administration** of 300 .mu.l of 1 mM CINN as a single bolus in mice caused a 2.3-fold increase in the PTT which remained 1.2-fold normal 2 h later. The BENZ and .alpha.-methyl-cinnamic acid (MECINN) esters were somewhat less effective as predicted from their in vitro effect on the PTT. This investigation and previous studies indicate that these compounds demonstrate low toxicity at therapeutic levels. It is concluded that the p-amidinophenyl esters may be useful in antithrombotic therapy.
SO Thrombosis and Haemostasis, (1986) 56/3 (387-390).
CODEN: THHADQ
AB Three p-amidinophenyl esters have been synthesized and characterized as irreversible **inhibitors** of the vitamin-K dependent proteinases; **factors IXa**, Xa and thrombin. In the present report we describe the in vitro and in vivo effects of these agents on. . . p-amidinophenyl ester of cinnamic acid (CINN) showed the most pronounced effect on both assays. This ester also is the best **inhibitor** of human **factors IXa** and Xa, while the p-amidinophenyl ester of benzoic acid (BENZ) is a slightly better .alpha.-**thrombin inhibitor**. The effect of these esters on the thrombin clotting time correlated with in vitro kinetic measurements of .alpha.-**thrombin inhibition** rates. Both BENZ and CINN increased the assay endpoint more than 6-fold. The three esters also were studied using mouse plasma. A comparable effect on the PTT was noted. Intravenous **administration** of 300 .mu.l of 1 mM CINN as a single bolus in mice caused a 2.3-fold increase in the PTT. . .

=> s pinsky D?/au or stern D?/au or Schmidt A?/au or Rose E?/au or solomon R?/au
L13 10574 PINSKY D?/AU OR STERN D?/AU OR SCHMIDT A?/AU OR ROSE E?/AU OR

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                SOLOMON R?/AU

=> s l13 and (factor IXa)
L14          89 L13 AND (FACTOR IXA)

=> dup rem l14
PROCESSING COMPLETED FOR L14
L15          37 DUP REM L14 (52 DUPLICATES REMOVED)

=> dis his

     (FILE 'HOME' ENTERED AT 10:07:42 ON 29 MAR 2001)

     FILE 'MEDLINE, CAPLUS, EMBASE, BIOSIS' ENTERED AT 10:07:58 ON 29 MAR 2001
L1         12853 S (FACTOR IXA) OR (FACTOR IX)
L2          3660 S L1 (P) (MUTAT? OR INHIB?)
L3        652552 S L2 (P) CLOT OR THROMB?
L4          1125 S L2 (P) (CLOT OR THROMB?)
L5           355 S L2 (P) (INHIBIT? (5N) (CLOT OR THROMB?))
L6             0 S L5 AND @PD<199609
L7             0 S L5 AND @PD<1999609
L8             0 S L5 AND @PD <1999609
L9             0 S L5 AND @PD < 1999609
L10          263 S L5 AND PD<19990927
L11          128 DUP REM L10 (135 DUPLICATES REMOVED)
L12            7 S L11 (P) ADMINIST?
L13        10574 S PINSKY D?/AU OR STERN D?/AU OR SCHMIDT A?/AU OR ROSE E?/AU OR
L14           89 S L13 AND (FACTOR IXA)
L15           37 DUP REM L14 (52 DUPLICATES REMOVED)

=> s  l15 and PD<19960927
'19960927' NOT A VALID FIELD CODE
   2 FILES SEARCHED...
   3 FILES SEARCHED...
L16           4 L15 AND PD<19960927

=> dis l16 1-4 ibib abs

L16  ANSWER 1 OF 4  BIOSIS  COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER:   1991:356261  BIOSIS
DOCUMENT NUMBER:    BR41:40776
TITLE:              ACTIVE SITE-BLOCKED FACTOR IXA PREVENTS
                    INTRAVASCULAR CORONARY THROMBOSIS WITHOUT IMPAIRING
                    EXTRAVASCULAR COAGULATION.
AUTHOR(S):          BENEDICT C R; RYAN J; GERLACH M; WOLITZKY B; STERN
                    D
CORPORATE SOURCE:   UNIV. TEXAS, HOUSTON, TEX.
SOURCE:             JOINT MEETING OF THE ASSOCIATION OF AMERICAN PHYSICIANS,
                    THE AMERICAN SOCIETY FOR CLINICAL INVESTIGATION, AND THE
                    AMERICAN FEDERATION FOR CLINICAL RESEARCH, SEATTLE,
                    WASHINGTON, USA, MAY 3-6, 1991. CLIN RES, (1991) 39 (2),
                    197A.
                    CODEN: CLREAS. ISSN: 0009-9279.
DOCUMENT TYPE:      Conference
FILE SEGMENT:       BR; OLD
LANGUAGE:           English

L16  ANSWER 2 OF 4  BIOSIS  COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER:   1987:58627  BIOSIS
DOCUMENT NUMBER:    BR32:28848
TITLE:              TUMOR NECROSIS FACTOR UPREGULATES FACTOR-IX-IXA BINDING
                    SITES AND FACTOR-IXA-VIII-MEDIATED
                    FACTOR-XA FORMATION ON ENDOTHELIUM.
AUTHOR(S):          NAWROTH P P; CORNELSON S; STERN D M
CORPORATE SOURCE:   OKLA. MED. RES. FOUND., OKLAHOMA CITY, OKLA.
SOURCE:             JOINT PROCEEDINGS OF THE 59TH SCIENTIFIC SESSIONS OF THE
                    AMERICAN HEART ASSOCIATION, THE 40TH ANNUAL MEETING OF THE
                    AMERICAN SOCIETY FOR THE STUDY OF ARTERIOSCLEROSIS (COUNCIL
                    ON ARTERIOSCLEROSIS), AND THE SEVENTH NATIONAL CONFERENCE
                    ON THROMBOSIS AND HEMOSTASIS, DALLAS, TEX., USA, NOV.
                    17-20, 1986. AM HEART ASSOC MONOGR, (1986) 0 (124), II-233.
                    CODEN: AHMOAH. ISSN: 0065-8499.
DOCUMENT TYPE:      Conference
FILE SEGMENT:       BR; OLD
LANGUAGE:           English

L16  ANSWER 3 OF 4  BIOSIS  COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER:   1986:194805  BIOSIS
DOCUMENT NUMBER:    BR30:106677
TITLE:              ACTIVATION OF COAGULATION RELEASES ENDOTHELIAL CELL
                    MITOGENS.
AUTHOR(S):          GAJDUSEK C; CARBON S; NAWROTH P; STERN D
CORPORATE SOURCE:   UNIV. WASH., SEATTLE, WASH.
SOURCE:             SYMPOSIUM ON PROTEASES IN BIOLOGICAL CONTROL AND
                    BIOTECHNOLOGY HELD AT THE 15TH ANNUAL UCLA (UNIVERSITY OF
                    CALIFORNIA-LOS ANGELES) MEETING ON MOLECULAR AND CELLULAR
                    BIOLOGY, LOS ANGELES, CALIF., USA, FEB. 9-15, 1986. J CELL
                    BIOCHEM SUPPL, (1986) 0 (10 PART A), 248.
                    CODEN: JCBSD7.
DOCUMENT TYPE:      Conference
FILE SEGMENT:       BR; OLD
LANGUAGE:           English

L16  ANSWER 4 OF 4  BIOSIS  COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER:   1984:77271  BIOSIS
DOCUMENT NUMBER:    BR26:77271
TITLE:              THE BINDING OF FACTOR-IX AND FACTOR-IXA
                    TO VASCULAR ENDOTHELIAL CELLS.
AUTHOR(S):          STERN D M; DRILLINGS M; NOSSEL H L
CORPORATE SOURCE:   DEP. MED., COLUMBIA UNIV. COLL. PHYSICIANS SURGEONS, NEW
                    YORK, USA.
SOURCE:             9TH INTERNATIONAL CONGRESS ON THROMBOSIS AND HEMOSTASIS,
                    JULY 4-8, 1983. THROMB HEMOSTASIS, (1983) 50 (1), 419.
                    CODEN: THHADQ. ISSN: 0340-6245.
DOCUMENT TYPE:      Conference
FILE SEGMENT:       BR; OLD
LANGUAGE:           English


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☐ 1. Document ID: US 6200749 B1

L7: Entry 1 of 12 File: USPT Mar 13, 2001

US-PAT-NO: 6200749
DOCUMENT-IDENTIFIER: US 6200749 B1

TITLE: Mutated forms of the ataxia-telangiectasia gene and method to screen for a partial A-T phenotype

DATE-ISSUED: March 13, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Shiloh; Yosef	Tel Aviv	N/A	N/A	ILX

US-CL-CURRENT: 435/6; 536/23.5

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

☐ 2. Document ID: US 6103244 A

L7: Entry 2 of 12 File: USPT Aug 15, 2000

US-PAT-NO: 6103244
DOCUMENT-IDENTIFIER: US 6103244 A

TITLE: Methods for generating immune responses employing modified vaccinia of fowlpox viruses

DATE-ISSUED: August 15, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Dorner; Friedrich	Vienna	N/A	N/A	ATX
Scheiflinger; Friedrich	Orth/Donau	N/A	N/A	ATX
Falkner; Falko Gunter	Mannsdorf	N/A	N/A	ATX
Pfleiderer; Michael	Breitstetten	N/A	N/A	ATX

US-CL-CURRENT: 424/199.1; 424/188.1, 424/232.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

☐ 3. Document ID: US 6093392 A

L7: Entry 3 of 12 File: USPT Jul 25, 2000

US-PAT-NO: 6093392
DOCUMENT-IDENTIFIER: US 6093392 A

TITLE: Methods and compositions for use in gene therapy for treatment of hemophilia

DATE-ISSUED: July 25, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
High; Katherine A.	Merion	PA	N/A	N/A
Herzog; Roland W.	Glenolden	PA	N/A	N/A

US-CL-CURRENT: 424/93.2; 424/93.6, 435/320.1, 435/456

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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☐ 4. Document ID: US 6046380 A

L7: Entry 4 of 12 File: USPT Apr 4, 2000

US-PAT-NO: 6046380
DOCUMENT-IDENTIFIER: US 6046380 A

TITLE: Factor IX production in transgenic non-human mammals and factor IX DNA sequences with modified splice sites

DATE-ISSUED: April 4, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Clark; Anthony John	Midlothian	N/A	N/A	GBX

US-CL-CURRENT: 800/14; 435/212, 435/69.6, 536/23.2, 536/23.5, 800/7

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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☐ 5. Document ID: US 6034222 A

L7: Entry 5 of 12 File: USPT Mar 7, 2000

US-PAT-NO: 6034222
DOCUMENT-IDENTIFIER: US 6034222 A

TITLE: Method for the separation of recombinant pro-factor IX from recombinant factor IX

DATE-ISSUED: March 7, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Fischer; Bernhard	Vienna	N/A	N/A	ATX
Mitterer; Artur	Orth/Donau	N/A	N/A	ATX
Dorner; Friedrich	Vienna	N/A	N/A	ATX
Eibl; Johann	Vienna	N/A	N/A	ATX

US-CL-CURRENT: 530/381; 530/412, 530/416

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWMC | Draw Desc | Image

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☐ 6. Document ID: US 6027913 A

L7: Entry 6 of 12 File: USPT Feb 22, 2000

US-PAT-NO: 6027913
DOCUMENT-IDENTIFIER: US 6027913 A

TITLE: Nucleic acid amplification with direct sequencing

DATE-ISSUED: February 22, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Sommer; Steven S.	Northwest Rochester	MN	55901	N/A

US-CL-CURRENT: 435/69.1; 435/91.21

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWMC | Draw Desc | Image

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☐ 7. Document ID: US 5891629 A

L7: Entry 7 of 12 File: USPT Apr 6, 1999

US-PAT-NO: 5891629
DOCUMENT-IDENTIFIER: US 5891629 A

TITLE: Compositions for improving RNase cleavage of base pair mismatches in double-stranded nucleic acids

DATE-ISSUED: April 6, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Goldrick; Marianna M.	Pflugerville	TX	N/A	N/A

US-CL-CURRENT: 435/6; 435/91.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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☐ 8. Document ID: US 5858661 A

L7: Entry 8 of 12 File: USPT Jan 12, 1999

US-PAT-NO: 5858661
DOCUMENT-IDENTIFIER: US 5858661 A

TITLE: Ataxia-telangiectasia gene and its genomic organization

DATE-ISSUED: January 12, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Shiloh; Yosef	Tel Aviv	N/A	N/A	ILX

US-CL-CURRENT: 435/6; 536/23.5

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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☐ 9. Document ID: US 5839443 A

L7: Entry 9 of 12 File: USPT Nov 24, 1998

US-PAT-NO: 5839443
DOCUMENT-IDENTIFIER: US 5839443 A

TITLE: Method for inhibiting thrombosis in a patient whose blood is subjected to extracorporeal circulation

DATE-ISSUED: November 24, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Rose; Eric	Tenafly	NJ	N/A	N/A
Stern; David	Great Neck	NY	N/A	N/A
Schmidt; Ann Marie	Franklin Lakes	NJ	N/A	N/A
Spanier; Talia	New York	NY	N/A	N/A

US-CL-CURRENT: 128/898; 435/13

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWMC | Draw Desc | Image

☐ 10. Document ID: US 5268275 A

L7: Entry 10 of 12 File: USPT Dec 7, 1993

US-PAT-NO: 5268275
DOCUMENT-IDENTIFIER: US 5268275 A

TITLE: Vitamin K-dependent carboxylase

DATE-ISSUED: December 7, 1993

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Stafford; Darrel W.	Carrboro	NC	N/A	N/A
Wu; Sheue-Mei	Carrboro	NC	N/A	N/A

US-CL-CURRENT: 435/69.1; 435/232, 435/252.3, 435/320.1, 435/352, 435/354, 435/358, 435/366, 435/69.6, 536/23.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWMC | Draw Desc | Image

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Terms	Documents
(Factor adj (IXa or IX)) near mutat$	12

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Search Results - Record(s) 1 through 10 of 12 returned.

☐ 1. Document ID: US 6200749 B1

L7: Entry 1 of 12 File: USPT Mar 13, 2001

DOCUMENT-IDENTIFIER: US 6200749 B1
TITLE: Mutated forms of the ataxia-telangiectasia gene and method to screen for a partial A-T phenotype

DEPR:
A technical explanation for this bias towards deletions and insertions could be a greater ability of the REF method to detect such lesions versus its ability to detect base substitution. Liu and Sommer (1995) have shown, however, that the detection rate of this method in a sample of 42 point mutations in the factor IX gene ranged between 88% and 100%, depending on the electrophoresis conditions. The 7 base substitutions detected directly by the REF method in the present study (Table 2), indicate that such sequence alterations are detected in our hands as well.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWMC | Draw Desc | Image

☐ 2. Document ID: US 6103244 A

L7: Entry 2 of 12 File: USPT Aug 15, 2000

DOCUMENT-IDENTIFIER: US 6103244 A
TITLE: Methods for generating immune responses employing modified vaccinia of fowlpox viruses

DEPR:
Human clotting factor IX is a 56 kDa glycoprotein involved in the regulation of blood coagulation. This clotting factor undergoes complex post-translational modifications: vitamin K dependent carboxylation of the first 12 glutamic residues, glycosylation, 3-hydroxylation of an aspartic acid and amino terminal protein processing. Davie, E. W., "The Blood Coagulation Factors: Their cDNAs, Genes and Expression", HEMOSTATIS AND THROMBOSIS, Colman et al., eds., J. B. Lippincott Co. (1987). Hemophilia B, an X chromosome-linked bleeding disorder, is caused by mutation of factor IX. Patients with hemophilia are currently treated by substitution with plasma-derived factor IX.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWMC | Draw Desc | Image

☐ 3. Document ID: US 6093392 A

L7: Entry 3 of 12 File: USPT Jul 25, 2000

DOCUMENT-IDENTIFIER: US 6093392 A
TITLE: Methods and compositions for use in gene therapy for treatment of hemophilia

BSPR:
In another aspect, the isolated DNA encoding Factor IX comprises a mutation which renders Factor IX encoded thereby incapable of binding to collagen IV.

BSPR:
In yet another aspect, the isolated DNA encoding Factor IX comprises a mutation which renders Factor IX encoded thereby incapable of binding to collagen IV.

CLPR:
7. The method of claim 1, wherein said nucleic acid encoding Factor IX comprises a mutation which reduces binding of Factor IX encoded thereby to collagen IV as compared to a Factor IX lacking the mutation, wherein the mutation replaces a lysine residue with an alanine residue in the fifth amino acid position from the beginning of mature Factor IX.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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☐ 4. Document ID: US 6046380 A

L7: Entry 4 of 12 File: USPT Apr 4, 2000

DOCUMENT-IDENTIFIER: US 6046380 A
TITLE: Factor IX production in transgenic non-human mammals and factor IX DNA sequences with modified splice sites

ORPL:
Chen, S.-H. et al., "Splice junction mutations in factor IX gene resulting in severe hemophilia B," Nucl. Acids Res. 19(5):1172 (1992).

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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☐ 5. Document ID: US 6034222 A

L7: Entry 5 of 12 File: USPT Mar 7, 2000

DOCUMENT-IDENTIFIER: US 6034222 A
TITLE: Method for the separation of recombinant pro-factor IX from recombinant factor IX

BSPR:
Up to now, an improvement in the recovery of recombinant, physiologically active Factor IX could only be achieved through genetic manipulation of the pro-sequence. It has thus been attempted to couple the pro-sequence of Factor VII to the DNA sequence of Factor IX in order to obtain a more effective cleavage of the pro-sequence (K. Berkner et al., Current Advances in Vitamin K Research, Elsevier Science Publishing Co., Inc. (1988) 199-207). P. Meulien et al., Prot. Engineer. 3 (1990) 629-633) examined the influence of mutations in the region of the pro-peptide cleavage site of Factor IX. They determined that the yield of active Factor IX can be distinctly increased by introduction of a point mutation in position +1 (alanine versus tyrosine); in comparison with wild-type Factor IX, which demonstrates a specific activity of 45-55% after purification over a DEAE-Sepherodex.RTM. column and stepwise elution with 0.3 M NaCl in the physiological pH range, a specific activity of 85 to 100% was found for the mutated Factor IX.

☐ 6. Document ID: US 6027913 A

L7: Entry 6 of 12 File: USPT Feb 22, 2000

DOCUMENT-IDENTIFIER: US 6027913 A
TITLE: Nucleic acid amplification with direct sequencing

DEPR:
Direct sequencing also makes it feasible to delineate point mutations in multiple individuals. For an X-linked lethal disease, direct sequencing can provide a "snapshot" of recent mutations in the population because the mutations that arise are extinguished within a few generations [Haldane, J. B. S., Genet, 31:317-326 (1935)]. Analysis of such data should reveal whether any hotspots of mutation exist. Previously protein and nucleic acid sequence of hundreds of variant .alpha.- and .beta.- globin alleles did not reveal any dramatic hotspots in these autosomal genes [Vogel, F. and A. G. Motulsky (eds) In: Human Genetics. Edition 2, Springer-Verlag, Berlin, pp. 433-511, (1986)). Notably, transitions of CpG were not markedly elevated. More recently the delineation of mutations in other genes has indicated that transitions at CpG occur with great frequency [Youssoufian, H., H. H. Kazazian, Jr., D. B. Phillips, S. Aronis, G. Tsifitis, V. A. Brown, S. E. Antonarkis, Nature, 324:380-382 (1986); Youssoufian, H., S. E. Antonarakis, W. Bell, A. M. Griffin, H. H. Kazazian, Jr., Am. J. Hum. Genet., 42:718-725 (1988); Vulliamy T. J., M. D. Urso, G. Battistuzzi, M. Estrada, N. S. Foulkes, G. Martini, V. Calabro, V. Poggi, R. Giordana, M. Town, L. Luzzato, M. G. Persico, Proc. Natl. Acad. Sci. USA, 85:5171-5175 (1988); Cooper D. N. and H. Youssoufian, Hum. Genet., 78:151-155 (1988)]. Eight regions of likely functional significance in 21 hemophiliacs from different families have been sequenced. The results of this large sample of germline mutations from a single gene show that CpG is a hotspot of mutation in the factor IX gene and that the rate of enhancement is about 77-fold. This enhancement is not restricted to a particular subset of CpGs with constant bases in the immediately flanking sequence.

☐ 7. Document ID: US 5891629 A

L7: Entry 7 of 12 File: USPT Apr 6, 1999

DOCUMENT-IDENTIFIER: US 5891629 A
TITLE: Compositions for improving RNase cleavage of base pair mismatches in double-stranded nucleic acids

BSPR:
Of the three mutations in the Factor IX model system that were not detected by either RNase A alone or the RNase A/RNase I combination used in the initial studies, all are detected using the new RNase digestion conditions disclosed in the present invention. Mutations in the p53 tumor suppressor gene that are not detected by RNase A are also detected by RNase I using the new conditions (FIG. 6A, FIG. 6B, and FIG. 6C). Moreover, when the entire panel of 60 mismatches in the model system (2 complementary mismatches are generated from each of the 30 point mutations) is compared using the new RNase digestion components and the components used in the method described in U.S. patent application Ser. No. 08/371,531, it is clear that the new conditions show a dramatic improvement in the general ability to specifically cleave a wide variety of mismatches.

DRPR:
FIGS. 7A-7B: Cleavage of mismatches in a large panel of homozygous and heterozygous samples with Factor IX mutations. FIG. 7 is composed of two panels: FIG. 7A and FIG. 7B.

DEPR:
This example details the cleavage and detection of mismatches with digestion buffers of the present invention in large panel homozygous and heterozygous samples with Factor IX mutations. Double-stranded RNA targets containing mismatches due to point mutations in exon 8 of the Factor IX gene were prepared from genomic DNA isolated from Hemophilia B patients and heterozygous carriers, as described in Example 2.

DEPC:
Cleavage of Mismatches in Large Panel of Homozygous and Heterozygous Samples with Factor IX Mutations

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

☐ 8. Document ID: US 5858661 A

L7: Entry 8 of 12 File: USPT Jan 12, 1999

DOCUMENT-IDENTIFIER: US 5858661 A
TITLE: Ataxia-telangiectasia gene and its genomic organization

DEPR:
A technical explanation for this bias towards deletions and insertions could be a greater ability of the REF method to detect such lesions versus its ability to detect base substitution. Liu and Sommer (1995) have shown, however, that the detection rate of this method in a sample of 42 point mutations in the factor IX gene ranged between 88% and 100%, depending on the electrophoresis conditions. The 7 base substitutions detected directly by the REF method in the present study (Table 2), indicate that such sequence alterations are detected in our hands as well.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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☐ 9. Document ID: US 5839443 A

L7: Entry 9 of 12 File: USPT Nov 24, 1998

DOCUMENT-IDENTIFIER: US 5839443 A
TITLE: Method for inhibiting thrombosis in a patient whose blood is subjected to extracorporeal circulation

DEPU:
Wacey, A. I., Krawczak, M., Kakkar, V. V. and Cooper, D. N. (1994) Determinants of the factor IX mutational spectrum in haemophilia B: an analysis of missense mutations using a multi-domain molecular model of the activated protein. Hum. Genet. 94:594-608.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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☐ 10. Document ID: US 5268275 A

L7: Entry 10 of 12 File: USPT Dec 7, 1993

DOCUMENT-IDENTIFIER: US 5268275 A
TITLE: Vitamin K-dependent carboxylase

DEPR:
Preparation of Affinity Column. Peptide FIXQ/S SEQ ID NO:1)(residues -18 to 41 of factor IX with mutations Arg to Glu at residue -4 and Arg to Ser at residue -1) was chosen for the affinity ligand because its affinity for the carboxylase is not changed and because it has fewer trypsin cleavage sites than our other peptides and is therefore less likely to be degraded by proteases in the crude extracts used for purification. Peptide FIXQ/S was prepared according to S.-M. Wu et al. supra. One hundred mg of FIXQ/S was coupled to 25 ml of Affi-Gel 10 (Bio-Rad Inc.) according to the manufacturer. The reaction was done at pH 4.8, which is one unit below the theoretical pI of FIXQ/S. The final concentration of the covalently bound FIXQ/S on Affi-Gel 10 was measured as 442 .mu.M and the coupled ligand is referred to as Affi-FIXQ/S.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

Generate Collection

Terms	Documents
(Factor adj (IXa or IX)) near mutat$	12

Display 10 Documents, starting with Document: 11

Display Format: KWIC Change Format

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Search Results - Record(s) 11 through 12 of 12 returned.

☐ 11. Document ID: US 4994371 A

L7: Entry 11 of 12 File: USPT Feb 19, 1991

US-PAT-NO: 4994371
DOCUMENT-IDENTIFIER: US 4994371 A

TITLE: DNA preparation of Christmas factor and use of DNA sequences

DATE-ISSUED: February 19, 1991

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Davie; Earl W.	Bellevue	WA	98004	N/A
Kurachi; Kotoku	Seattle	WA	98125	N/A

US-CL-CURRENT: 435/6; 435/243, 435/320.1, 435/91.41, 435/91.51, 436/501, 436/504, 536/23.5, 536/24.31, 536/25.32

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

☐ 12. Document ID: CA 2002540 C, EP 373012 A, FR 2638643 A, CA 2002540 A, JP 02265487 A, EP 373012 B1, DE 68920980 E, US 5521070 A, JP 2936201 B2

L7: Entry 12 of 12 File: DWPI Apr 4, 2000

DERWENT-ACC-NO: 1990-180758
DERWENT-WEEK: 200035

TITLE: DNA coding for human factor IX - with mutation in pro coding sequence

INVENTOR: MEULIEN, P

PRIORITY-DATA: 1988FR-0014635 (November 9, 1988)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
CA 2002540 C	April 4, 2000	F	000	C12N015/57
EP 373012 A	June 13, 1990	N/A	000	N/A
FR 2638643 A	May 11, 1990	N/A	000	N/A
CA 2002540 A	May 9, 1990	N/A	000	N/A
JP 02265487 A	October 30, 1990	N/A	000	N/A
EP 373012 B1	February 1, 1995	F	011	C12N015/57
DE 68920980 E	March 16, 1995	N/A	000	C12N015/57
US 5521070 A	May 28, 1996	N/A	007	C12N015/00
JP 2936201 B2	August 23, 1999	N/A	012	C12N015/09

INT-CL (IPC): A61K 31/00; A61K 37/54; A61K 38/43; A61K 38/46; C07H 21/04; C07K 14/00; C07K 15/06; C12N 5/10; C12N 9/64; C12N 15/00; C12N 15/09; C12N 15/57; C12N 15/86; C12P 9/00; C12P 21/00; C12P 21/02; C12P 21/06; C12R 1/91

WEST

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Search Results - Record(s) 11 through 12 of 12 returned.

☐ 11. Document ID: US 4994371 A

L7: Entry 11 of 12 File: USPT Feb 19, 1991

DOCUMENT-IDENTIFIER: US 4994371 A
TITLE: DNA preparation of Christmas factor and use of DNA sequences

DEPR:
In accordance with the subject invention, DNA sequences are provided for hybridization with pro-factor IX, factor IX, factor IX.sub.a, and activation peptide, and for DNA and RNA fragments which can be used in the detection of mutations or other genetic deficiencies concerned with factor IX. The sequences can be used in diagnosing blood clotting deficiencies, such as hemophilia, particularly hemophilia B. By lysing cells as described above and screening the DNA with fragments according to the subject invention, mutations in the factor IX gene may be determined.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

☐ 12. Document ID: CA 2002540 C, EP 373012 A, FR 2638643 A, CA 2002540 A, JP 02265487 A, EP 373012 B1, DE 68920980 E, US 5521070 A, JP 2936201 B2

L7: Entry 12 of 12 File: DWPI Apr 4, 2000

DERWENT-ACC-NO: 1990-180758
DERWENT-WEEK: 200035

TITLE: DNA coding for human factor IX - with mutation in pro coding sequence

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

Generate Collection

Terms	Documents
(Factor adj (IXa or IX)) near mutat$	12

Display 10 Documents, starting with Document: 12

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Search for additional matches among the next 2000 terms

starting with: INHIB$(INHIBITS/INCREASES).P28-P85,P87-P87,P23-P27,P20-P22,P1-P18.

Search Results -

Terms	Documents
((Factor adj (IXa or IX)) near (mutat$ or mutein$)) same administ$ same inhib$	0

Database: US Patents Full-Text Database; US Pre-Grant Publication Full-Text Database; JPO Abstracts Database; EPO Abstracts Database; Derwent World Patents Index; IBM Technical Disclosure Bulletins

Refine Search: ((Factor adj (IXa or IX)) near (mutat$ or mutein$)) same administ$ same inhib$ Clear

Search History

Today's Date: 3/29/2001

DB Name	Query	Hit Count	Set Name
USPT,PGPB,JPAB,EPAB,DWPI	((Factor adj (IXa or IX)) near (mutat$ or mutein$)) same administ$ same inhib$	0	L6
USPT,PGPB,JPAB,EPAB,DWPI	((Factor adj (IXa or IX)) near (mutat$)) same administ$ same inhib$	0	L5
USPT,PGPB,JPAB,EPAB,DWPI	((Factor adj (IXa or IX)) near (mutat$)) same administ$ same (clot or thromb$)	0	L4
USPT,PGPB,JPAB,EPAB,DWPI	((Factor adj (IXa or IX)) near (mutat$)) near administ$ same (clot or thromb$)	0	L3
USPT,PGPB,JPAB,EPAB,DWPI	(Factor adj (IXa or IX)) near (mutat$) near administ$ near (clot or thromb$)	0	L2
USPT,PGPB,JPAB,EPAB,DWPI	(Factor adj (IXa or IX)) near (mutat?) near administ? near clot	0	L1

For 09/053,871

L10 ANSWER 8 OF 15 MEDLINE
AB . . . Russell's Viper Venom time and by the Textarin/Ecarin ratio. APC-response was studied by a clotting (aPTT-based) and by an amidolytic (**factor IXa**-X-based) assay. A reduced response to APC (APC-resistance) was found in 49% of 65 PLa-positive and in 13% of 90 PLa-negative. . . common in the samples with LA, as compared to CLa+PSa positive (58% vs. 30%, not significant). The presence of the **mutation** causing Arg506-Gln substitution in coagulation factor V was investigated in 84 samples. The occurrence of the **mutation** in APC-resistant patients with CLa+PSa or with LA in one of the two assays was similar to those without PLa (84% and 100%, respectively). In the absence of APC resistance, the occurrence of the **mutation** was similar in the samples with and without PLa (14% vs. 11%). Samples with LA, determined by both tests used, comprised a special group where the frequency of the **mutation** in the APC resistant samples was significantly reduced ($p < 0.01$). In the latter samples, the pathogenic mechanism of APC. . .
CT . . .
V Deficiency: BL, blood
*Factor V Deficiency: GE, genetics
Factor V Deficiency: IM, immunology
IgG: IM, immunology
IgM: IM, immunology
Lupus Coagulation Inhibitor: AN, analysis
Middle Age
Molecular Sequence Data
*Partial Thromboplastin Time
Phosphatidylserines: IM, immunology
*Phospholipids: IM, immunology
*Point. . .
CN 0 (Antibodies, Anticardiolipin); 0 (Antibodies, Antiphospholipid); 0 (IgG); 0 (IgM); 0 (Lupus Coagulation **Inhibitor**); 0 (Phosphatidylserines); 0 (Phospholipids); 0 (Protein C)

L10 ANSWER 9 OF 15 MEDLINE
AB To elucidate the role of the P1' residue of the serpin, antithrombin (AT), in proteinase **inhibition**, the source of the functional defect in a natural Ser-394-->Leu variant, AT-Denver, was investigated. AT-Denver **inhibited** thrombin, **Factor IXa**, plasmin, and Factor Xa with second order rate constants that were 430-, 120-, 40-, and 7-fold slower, respectively, than those of native AT, consistent with an altered specificity of the variant **inhibitor** for its target proteinases. AT-Denver **inhibited** thrombin and Factor Xa with nearly equimolar stoichiometries and formed SDS-stable complexes with these proteinases, indicating that the diminished **inhibitor** activity was not due to an enhanced turnover of the **inhibitor** as a substrate. Binding and kinetic studies showed that heparin binding to AT-Denver as well as heparin accelerations of AT-Denver-proteinase reactions were normal, consistent with the P1' **mutation** not affecting the heparin activation mechanism. Resolution of the two-step reaction of AT-Denver with thrombin revealed that the majority of. . . was localized in the second reaction step and resulted from a 190-fold decreased rate constant for conversion of a noncovalent proteinase-**inhibitor** encounter complex to a stable, covalent complex. Little or no effects of the **mutation** on the binding constant for

encounter complex formation or on the rate constant for stable complex dissociation were evident. These. . . a role for the P1' residue of antithrombin in transition-state stabilization of a substrate-like attack of the proteinase on the **inhibitor**-reactive bond following the formation of a proteinase-**inhibitor** encounter complex but prior to the conformational change leading to the trapping of proteinase in a stable, covalent complex. Such. . .

L10 ANSWER 10 OF 15 MEDLINE
AB The purpose of this study is to determine which residues of the **factor IXa** heavy chain are important for interaction with the cofactor of **factor IXa**, **factor** VIIIa. Because the monoclonal antibody (MoAb) FXC008 **inhibits** interaction between **factors IXa** and VIIIa, and because it also reacts with residues 181-310 of the **factor IXa** heavy chain, we used the computer-modelled structure of the **factor IXa** heavy chain to select charged surface residues likely to interact with FXC008 and/or factor VIIIa. We made **mutations** in the region of residues 181-310 of the heavy chain of factor IX, and replaced these amino acids individually with those located at the same position in factor X. The **mutated** factor IX retained complete clotting activity and thus interacted normally with factor VIIIa. Five mutant proteins (factor IXK214F, factor IXK228R,. . . IXD276K nor factor IXR248H bound to FXC008. Factor IXR252V had reduced affinity to FXC008. Our results suggest the following: (1) **factor IXa** residues 214, 228, 240, 247, 248, 252, 260, and 276 are not involved in specific interaction with factor VIIIa; and. . .

L10 ANSWER 11 OF 15 MEDLINE
AB Inherited resistance to activated protein C (APC) is a recently identified major cause of thrombosis. It is associated with a **mutation** in the factor V gene affecting one of the cleavage sites for APC. APC resistance was recently found to be. . . in a purified system. The APC-mediated degradation of factor VIIIa was monitored by a factor X activation reaction using purified **factor IXa**, phospholipid, and calcium. In the presence of both factor V and protein S, APC was found to **inhibit** factor VIIIa activity efficiently. APC alone or together with factor V was ineffective, whereas APC in combination with protein S. . . in the reaction. Two monoclonal antibodies, one against protein S and the other directed toward factor V, were found to **inhibit** the APC cofactor activity of the factor V-protein S mixture. Factor Va did not express APC cofactor activity, and addition of excess factor Va over factor V did not **inhibit** the APC cofactor function of a factor V-protein S mixture. In conclusion, the results suggest that factor V and protein. . .

L10 ANSWER 12 OF 15 MEDLINE
AB Factor IX is a multidomain protein and is the proenzyme of a serine protease, **factor IXa**, essential for hemostasis. In this report, we describe the molecular basis of hemophilia B (deficiency of factor IX activity) in. . . rearrangements of the factor IX gene. By enzymatic amplification and sequencing of all exons and promoter regions, the following causative **mutation** in the protease domain of factor IX was identified in each patient: IXSchmallenberg: nucleotide 31,215G----T, Ser365Ile; IXVarel: nucleotide 31,214A----G, Ser365Gly;. . . Arg248Gln; and IXMonschau: nucleotide 30,855A----T, Glu245Val. In IXVarel, nucleotide 31,213T was also replaced by C, which results in a silent **mutation** (GAT----GAC) at Asp-364. Thus, this patient has a double base-pair substitution of TA to CG at nucleotides 31,213 and 31,214. . . 40% to 100% except for IXDreihacken (Arg248Gln), in which case it was approximately 4% of normal. The Ser365Gly and Ser365Ile **mutants** are nonfunctional because of lack of the active site serine residue. Mutant Asp364His is inactive because it cannot form the.

. . observed in other homologous serine proteases, this hydrogen bond is essential for maintaining the correct active site conformation in normal **factor IXa** (IXaN). Purified Arg248Gln had approximately 41% and Glu245Val had approximately 17% of the activity of normal factor IX (IXN) in. . . mutant did and the Arg248Gln mutant did not bind to an anti-IXN monoclonal antibody that has been shown previously to **inhibit** the interaction of factor VIIIa with factor IXaN. We have recently shown that a high-affinity calcium binding site exists in. . .

L10 ANSWER 13 OF 15 MEDLINE
AB . . . IX. Also, after treatment with factor XIa, none of the Bm variants reacted with antithrombin III (in contrast to normal **factor IXa**). Purified factor IX Deventer (one of the variants with a replacement of Arg181), either with or without pretreatment with factor XIa, was found to be a more effective competitive **inhibitor** of the factor VIIa-tissue factor-induced factor X activation than similarly treated normal factor IX. In addition, this **inhibitory** effect was much more pronounced when bovine tissue factor was used instead of human tissue factor. We propose that the. . . site serine that allows efficient substrate binding and catalysis, but that the same conformational change is instrumental in effectively dissociating **factor IXa** from the activating factor VIIa-tissue factor complex. Amino acid replacements that disrupt this conformational transition directly (e.g. Pro368----Thr near the catalytic center) or indirectly (**mutations** at the Arg180-Val activation site) therefore lead to a combination of 1) the loss of coagulant activity and 2) an **inhibitory** effect in the ox brain prothrombin time assay.
CT . . .
*Factor IX: GE, genetics
Factor IX: IM, immunology
Factor IX: ME, metabolism
Factor IX: PD, pharmacology
Factor VIIa: ME, metabolism
Factor X: AI, antagonists & inhibitors
Factor XIa: ME, metabolism
*Hemophilia A: BL, blood
Molecular Sequence Data
Molecular Weight
*Mutation
. . .

L10 ANSWER 14 OF 15 MEDLINE
AB Factor IX is the zymogen of the serine protease **factor IXa** involved in blood coagulation. In addition to a catalytic domain homologous to the chymotrypsin family, it has Ca2+, phospholipid, and. . . and beta-OH aspartic acid content, and in its binding to an anti-IXN monoclonal antibody which has been shown previously to **inhibit** the interaction of factor VIIIa with factor IXaN. Further, IXER is cleaved to yield a **factor IXa**-like molecule by factor XIa/Ca2+ at a rate similar to that observed for IXN. However, in contrast to IXaN, IXaER does not bind to antithrombin-III (specific **inhibitor** of IXaN) and does not catalyze the activation of factor X (substrate) to factor Xa. To identify the **mutation** in IXER, all eight exons of IXN and IXER gene were amplified by the polymerase chain reaction technique and cloned. A single point **mutation** (G----T) which results in the replacement of Val for Gly363 in the catalytic domain of IXER was identified. Gly363 in **factor IXa** corresponds to the universally conserved Gly193 in the active site sequence of the chymotrypsin serine protease family. X-ray crystallographic data. . . Our computer structural data support a

concept that the Gly363----Val change prevents the development of the active site conformation in **factor IXa** such that the substrate binding site and the oxyanion hole are not formed in the **mutated** enzyme.

L10 ANSWER 15 OF 15 MEDLINE

TI Replacement of isoleucine-397 by threonine in the clotting proteinase **factor IXa** (Los Angeles and Long Beach variants) affects macromolecular catalysis but not L-tosylarginine methyl ester hydrolysis. Lack of correlation between the ox brain prothrombin time and the **mutation** site in the variant proteins.

AB . . . two non-functional Factor IX variants, namely Los Angeles (IXLA) and Long Beach (IXLB). Both variants could be cleaved to yield **Factor IXa**-like molecules, but were defective in catalysing the cleavage of Factor X (macromolecular substrate) and in binding to antithrombin III (macromolecular **inhibitor**). In the present study we have identified the **mutation** of IXLA by amplifying the exons (including flanking regions) as well as the 5' end of the gene by polymerase-chain-reaction. . . substitution (T----C) in exon VIII of IXLA, with a predicted replacement of Ile-397 to Thr in the mature protein. This **mutation** is the same as found recently for IXLB. The observation that IXLB and IXLA have the same **mutation** is an unexpected finding, since, on the basis of their ox brain prothrombin time (PT, a test that measures the ability of the variant Factor IX molecules to **inhibit** the activation of Factor X by Factor VIIa-tissue factor complex), these variants have been classified into two different groups and. . . thought to be genetically different.

Our observation thus suggests that the ox brain PT does not reflect the locus of **mutation** in the coding region of the variant molecules. However, our analysis suggests that the ox brain PT is related to Factor IX antigen concentration in the patient's plasma. Importantly, although the **mutation** in IXLA or IXLB protein is in the catalytic domain, purified IXaLA and IXaLB hydrolyse L-tosylarginine methyl ester at rates. . . data on Factor IXBm Lake Elsinore (Ala-390----Val mutant), strengthen a conclusion that the peptide region containing residues 390-397 of normal **Factor IXa** plays an essential role in macromolecular substrate catalysis and **inhibitor** binding. However, the two **mutations** noted thus far in this region do not distort S1 binding site in the **Factor IXa** enzyme.